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Photoactivation mechanism of DNA photolyase

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Changes and damages in the DNA structure, such as, excision or modification of bases or alternation of sugar-phosphate groups are often caused by UV light, ionizing radiation, toxic substances and environmental pollution. To maintain genetic stability, cells protect themselves against these kinds of damages. Moreover, the main DNA repair processes in prokaryotic and eukaryotic cells are quite similar.

The DNA photolyases repair the most common type of the DNA defects – cyclobutane pyrimidine dimers (CPD) and (6-4)-photoproducts. The enzyme contains two photoactive cofactors, folic acic and $FADH^-$, which both can get in the excited state [1]. Folate cofactor plays a role of a photon antenna molecule, which harvests and transfers the excitation energy to the catalytically active $FADH^-$ form. The electron transfer from the excited $FADH^{*-}$ state to the pyrimidine dimer causes a splitting of the cyclobutane ring and back electron transfer to $FADH^{\bullet}$. Thus, photolyase repairs UV (200-300 nm) induced damage in DNA by splitting the ring of the CPD dimer into pyrimidine monomers [2, 3].

This presentation is on the theoretical computational study of the DNA photolyase from *E. coli*. Continuum electrostatic method [4] is employed to get a full insight into the photoactivation mechanism of the enzyme. Protonation state of titratable residues, the redox potentials of tryptophan triad, energetics and the reaction rates are calculated and compared with available experimental data. The free energies of all potentially relevant states for the radical transfer during the photoactivation process are evaluated.

Besides a general introduction to the photoactivation and photorepair mechanism, and the structure-function interrelation in the DNA photolyase, this presentation will also address a several long-time controversial questions, such as: Why is photolyase one of very few FAD containing proteins which resting (ground) state is a radical state $FADH^{\bullet}$? What is the distance between the CPD dimer and redox-active cofactor in the CPD–protein complex? Why does FADH cofactor adopt a quite unusual U-shape and what is the functional purpose of having such a form? Hopping vs. super-exchange mechanism of the ET pathway in the photoactivation process of FADH chromophore?

The obtained results are in very good agreement with the experiments [3, 5] and may be relevant for all other types of photolyases and cryptochromes, since they have a high degree of the sequence similarity including the conserved tryptophan triad present in all of these structures [6].

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